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KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK,  
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SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,  
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For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.

(54) Title: SUBSTITUTED PIPERAZINES, (1,4) DIASZEPINES, AND 2,5-DIAZABICYCLO (2.2.1) HEPTANES AS  
HISTAMINE H1 AND/OR H3 ANTAGONISTS OR HISTAMINE H3 REVERSE ANTAGONISTS

(57) Abstract: The present invention relates to novel piperazine and azepine derivatives having pharmacological activity, processes  
for their preparation, to compositions containing them and to their use in the treatment of neurodegenerative disorders including  
Alzheimer's disease.

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## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 03/11423

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D295/18 C07D317/68 C07D307/85 C07D405/06 C07D243/08  
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According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02 12214 A (ORTHO MCNEIL PHARM INC) 14 February 2002 (2002-02-14) cited in the application Abstract; page 4; claims; examples 7,8,24,26,27,53,88,90,91. ---	1-8
X	WO 02 06223 A (ABBOTT LAB) 24 January 2002 (2002-01-24) Abstract; claims; examples 162,163. ---	1-8
X	WO 02 12190 A (ORTHO MCNEIL PHARM INC) 14 February 2002 (2002-02-14) Abstract; page 4; claims; examples 50,59,61,62,71. --- -/--	1-8

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

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03/02/2004

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# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 03/11423

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 A61P11/00 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02 076925 A (BEAVERS LISA SELSAM; SCHAUS JOHN MEHNERT (US); WATSON BRIAN MORGAN) 3 October 2002 (2002-10-03) Abstract; claims, in particular compounds 102-105, 112-115 of claim 7.	1-8
P, X	WO 03 059341 A (ABBOTT LAB) 24 July 2003 (2003-07-24) Abstract; claims; examples 162, 163.	1-8
P, X	WO 03 066604 A (BOEHRINGER INGELHEIM INT; DOERWALD FLORENCIO ZARAGOZA (DK); PETTER) 14 August 2003 (2003-08-14) Abstract; claims; example 147.	1-8

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Name and mailing address of the ISA

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# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP 03/11423

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claim 7 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0212214	A	14-02-2002	US 2002065278 A1	30-05-2002
			AU 8111901 A	18-02-2002
			AU 8112101 A	18-02-2002
			AU 8473301 A	18-02-2002
			CA 2418369 A1	14-02-2002
			CA 2419027 A1	14-02-2002
			CA 2419036 A1	14-02-2002
			CN 1468221 T	14-01-2004
			CN 1468227 T	14-01-2004
			CZ 20030685 A3	13-08-2003
			CZ 20030686 A3	13-08-2003
			EP 1311499 A2	21-05-2003
			EP 1311482 A2	21-05-2003
			EP 1313721 A2	28-05-2003
			HU 0302893 A2	29-12-2003
			HU 0302959 A2	29-12-2003
			WO 0212224 A2	14-02-2002
			WO 0212214 A2	14-02-2002
			WO 0212190 A2	14-02-2002
			US 2002040024 A1	04-04-2002
			US 2002037896 A1	28-03-2002
WO 0206223	A	24-01-2002	AU 7338401 A	30-01-2002
			CA 2415396 A1	24-01-2002
			EP 1301480 A1	16-04-2003
			WO 0206223 A1	24-01-2002
WO 0212190	A	14-02-2002	US 2002040024 A1	04-04-2002
			AU 8111901 A	18-02-2002
			AU 8112101 A	18-02-2002
			AU 8473301 A	18-02-2002
			CA 2418369 A1	14-02-2002
			CA 2419027 A1	14-02-2002
			CA 2419036 A1	14-02-2002
			CN 1468221 T	14-01-2004
			CN 1468227 T	14-01-2004
			CZ 20030685 A3	13-08-2003
			CZ 20030686 A3	13-08-2003
			EP 1311499 A2	21-05-2003
			EP 1311482 A2	21-05-2003
			EP 1313721 A2	28-05-2003
			HU 0302893 A2	29-12-2003
			HU 0302959 A2	29-12-2003
			WO 0212224 A2	14-02-2002
			WO 0212214 A2	14-02-2002
			WO 0212190 A2	14-02-2002
			US 2002037896 A1	28-03-2002
			US 2002065278 A1	30-05-2002
WO 02076925	A	03-10-2002	CA 2441080 A1	03-10-2002
			EP 1379493 A2	14-01-2004
			WO 02076925 A2	03-10-2002
WO 03059341	A	24-07-2003	US 2002137931 A1	26-09-2002
			WO 03059341 A1	24-07-2003
WO 03066604	A	14-08-2003	WO 03066604 A2	14-08-2003
			US 2003236259 A1	25-12-2003